PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FP2455	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/SG2004/000380	International filing date *(day/month/year)* 22 November 2004	Priority date *(day/month/year)* 21 November 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl. ***A61F 2/28*** (2006.01) ***A61L 27/56*** (2006.01)
A61L 27/18 (2006.01) ***A61L 27/58*** (2006.01)

Applicant

NATIONAL UNIVERSITY OF SINGAPORE et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of **14** sheets, as follows:
      [X] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19 September 2005	11 January 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **ISOBEL TYSON** Telephone No. (02) 6283 2281

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SG2004/000380

Box No. I Basis of the report

1. With regard to the language, this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (under Rules 12.3(a) and 23.1 (b))

[ ] publication of the international application (under Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages **1-4, 6-10, 14-17, 19-37** as originally filed/furnished

pages* **5, 11-13, 18** received by this Authority on **19 September 2005** with the letter of **19 September 2005**

pages* received by this Authority on with the letter of

[X] the claims:

pages as originally filed/furnished

pages* as amended (together with any statement) under Article 19

pages* **38-46** received by this Authority on **19 September 2005** with the letter of **19 September 2005**

pages* received by this Authority on with the letter of

[X] the drawings:

pages **1/32-32/32** as originally filed/furnished

pages* received by this Authority on with the letter of

pages* received by this Authority on with the letter of

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/figs

[ ] the sequence listing *(specify)*:

[ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/figs

[ ] the sequence listing *(specify)*:

[ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SG2004/000380

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims 1-83	YES
	Claims	NO
Inventive step (IS)	Claims 1-83	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-83	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

This International Preliminary Report on Patentability is based on the following documents identified in the International Search Report:

- D1 = WO 1993/015682 A (AMERICAN CYANAMID COMPANY), 19 August 1993
- D2 = US 2002/0183858 A1 (CONTILIANO et al.), 5 December 2002
- D4 = US 2003/0100947 A1 (NADLER et al.), 29 May 2003
- D5 = WO 2001060288 A1 (ISOTIS N.V.), 23 August 2001
- D6 = US 5,383,932 A (WILSON et al.), 24 January 1995
- D7 = Patent Abstracts Japan, JP 09-173435 (TAKIRON CO LTD), 8 July 1997

NOVELTY (N) and INVENTIVE STEP (IS):

Claims 1-83 are considered novel and inventive in light of the above documents in that they neither disclose nor teach toward the present claimed invention.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 83 is not clear in that it purports to a kit, but the only constituent is the plug implant of Claims 1-44. Claim 83 is therefore of the same scope as Claims 1-44.

by layer using, for example, the Fused Deposition Modeling (FDM) technology.

The PLC filament layers of the plug implant may have an orientation of 0 degree, 60 degree and/or 120 degree.

According to a further embodiment, the plug implant comprises an opening for placement and removal of a catheter for drainage.

In particular, the plug implant is suitable to be inserted into a defect or a gap of a bone and the plug implant does not require means for fixing the plug to the external surface of the bone.

The plug implant may further comprise a bioactive agent.

The invention further provides a method for bone tissue regeneration comprising the steps of:

providing a bioabsorbable plug implant, wherein the implant comprises a first portion and a second portion extending outwardly from the first portion, the first and second portions formed from expandable material;

inserting the first portion into a defect or gap of a bone, the second portion engaging the outside contour of the defect or gap;

allowing the plug implant to contact body fluids, thereby expanding the size of the plug implant so that the plug fits into the defect or gap.

In the method of the invention, the implant may comprise a first and a second surface, opposite to each other, the first surface having an area smaller than the area of the second surface.

expandable material from which the plug implant is made may also be indicated as "scaffold".

In particular, the present invention discloses a bioabsorbable plug implant suitable for bone tissue regeneration, wherein the implant comprises a first portion, and a second portion extending outwardly from the first portion, the first and second portions formed from expandable material.

The plug implant of the invention may have any shape suitable to be inserted into a defect of a bone, for example, the plug implant may be shaped like a cone, truncated-cone, a pentahedron, a truncated-pentahedron, and/or a button mushroom.

According to a particular aspect of the plug implant of the invention, the first portion comprises a first surface, and the second portion comprises a second surface, opposite to the first, the first surface having an area smaller than the area of the second surface. The first and the second surfaces of the plug implant may have circular, square or rectangular shapes. The first and second surfaces may be plane surfaces.

The plug implant of the invention is made of a material which expand in contact with hydrophilic solution, hydrophilic liquid and/or body fluid.

Figure 1 show a skull (1) phantom comprising a burr hole (2), which for the purpose of the invention may be distinguished as defect (2) or gap (2).

With reference to Figure 2, which demonstrates an embodiment of the present invention, the plug implant can be shape like a "button mushroom" (3), comprising a first portion (5), and a second portion (4) extending outwardly from the first portion, the first and second portions formed from expandable material. The plug implant of the invention however is not limited to the shape of a button mushroom but may have any shape suitable to be inserted into a

defect of a bone, for example, the plug implant may be shaped like a cone, truncated-cone, a pentahedron, a truncated-pentahedron, and/or a button mushroom.

More in particular, in the embodiment exemplified in Figure 2, the first portion (5) comprises a first surface (5), and the second portion (4) comprises a second surface (4), opposite to the first, the first surface having an area smaller than the area of the second surface. In Figure 2, The first and the second surfaces of the plug implant have circular shapes. The first and second surfaces have plane surfaces. However, the shape is not limited to a circular one, but may be for example, a square or rectangular shape. Similarly, the surfaces is not limited to a place surface but may have any surface suitable for the purpose of the present invention, for example, an irregular, conical, acute, or elliptical shape may be within the scope of the present invention.

The first and second portions may also be characterized according to their thickness. In particular, the first portion (5) comprises the first surface and has a thickness X, whilst the second portion (4) comprises the second surface and has a thickness Y, the ratio X:Y being from 1:1 to 10:1. More in particular, in Figure 2, the ratio X:Y is 11:4, that is, the first portion (5) comprises 11 layers, whilst the second portion (4) comprises 4 layers. The number of layers may be chosen by the skilled person according to the particular shape of the plug implant and according to the type of bone, burr hole, and particular conditions of the patient, human or animal. As a particular example, the plug implant can be designed in such a way to such that a second portion may have thickness of 1 mm and the first portion thickness 3 mm.

Figure 3 is an isometric view of the embodiment of Figure 2. More in particular, Figure 3 shows the layered-scaffold structure made formed from biodegradable polymer filaments.

According to a further embodiment, the plug implant of the invention has a tapered shape or may have any shape suitable to be inserted into a defect of a bone, for example, the plug implant may be shaped like a cone, truncated-cone, a pentahedron, a truncated-pentahedron, and/or a button mushroom.

Figure 4(A) shows a plug implant having a tapered shape comprising a first portion (50) comprising a first surface (50), and the second portion (40) comprising a second surface (40), opposite to the first surface, the first surface (50) having an area smaller than the area of the second surface (50). The first portion (50) plug implant is inserted into the bone defect or gap whilst the second portion (40) engages with the contour of the defect or gap avoiding the plug implant to penetrate into the bone cavity.

The first and the second surfaces of the plug implant may have circular, square or rectangular shapes. The first and second surfaces may be plane surfaces.

Figure 4(B) shows the embodiment of Figures 2 and 3.

The size of the plug implant according to any embodiment of the invention as well as the first and second portion can be chosen by the skilled person according to the size of the bone defect or gap. For example, the plug implant can be designed in such a way to such that a second portion may have thickness of 1 mm and the first portion thickness 3 mm. The plug implant may have for example a diameter of the first portion of 15 mm and the diameter of the second portion of 20 mm (see Figures 2 and 3).

The particular shape of the plug of the invention in combination with the material which is a material which is expandable or swell (for example polycaprolactone (PCL)) at contact with at contact with hydrophilic solution, hydrophilic liquid and/or body fluid allows the plug implant to 'snap fit' into the defect or gap without the need of means for attaching the plug to the bone.

inserting the first portion into a defect or gap of a bone, the second portion engaging the outside contour of the defect or gap;

allowing the plug implant to contact body fluids, thereby expanding the size of the plug implant so that the plug fits into the defect or gap.

In the method of the invention, the implant may comprise a first and a second surface, opposite to each other, the first surface having an area smaller than the area of the second surface.

In the method of the invention, the plug implant may be formed from a porous material allowing the bone cells to penetrate into the plug implant and to regenerate the bone tissue. The plug implant may be shaped like a cone, truncated-cone, a pentahedron, a truncated-pentahedron, and/or a button mushroom. For instance, the first and second surface may have plane surfaces. Furthermore, the first and the second surfaces may have circular, square or rectangular shapes

In the method of the invention, the plug implant may be formed from a porous material allowing the bone cells to penetrate into the plug implant and to regenerate the bone tissue.

The method of the invention can be used for bone tissue regeneration and bone reparation for any kind of bone structure, however, it is particularly suitable for performing cranioplasty.

According to the method, plug implant and the bone defect or gap have an initial tolerance of less than 1 mm. In particular, the initial tolerance is less than 0.5 mm. Preferably, the initial tolerance is less than 0.2 mm.

The method of the invention may also comprises placing catheter into an opening of the plug implant for performing drainage.

Claims

1. A bioabsorbable plug implant, suitable for bone tissue regeneration, comprising a first portion, and a second portion extending outwardly from the first portion, the first and second portions formed from expandable material, and wherein the expandable material is a porous material.

2. The plug implant of claim 1, wherein the plug implant has a completely interconnected porous architecture.

3. The plug implant of the claims 1 to 2, wherein the plug implant is shaped like a cone, truncated-cone, a pentahedron, a truncated-pentahedron, and/or a button mushroom.

4. The plug implant of claims 1to 3, wherein the first portion comprises a first surface, and the second portion comprises a second surface, opposite to the first, the first surface having an area smaller than the area of the second surface.

5. The plug implant of claims 1to 4, wherein the first and second surface are plane surfaces.

6. The plug implant of claims 1to 5, wherein the first and the second surfaces have circular, square or rectangular shapes.

7. The plug implant of claims 1to 5, wherein the plug implant has a tapered shape.

8. The plug implant of claims 1to 7, wherein the first portion has a thickness X, and the second portion has a thickness Y, the ratio X:Y being from 1:1 to 10:1

Amended Sheet
IPEA/AU

9. The plug implant of claims 1to 8, wherein the expandable material comprises bioresorbable polycaprolactone (PLC).

10. The plug implant of claim 9, wherein the expandable material is prepared by layering PLC filaments layer by layer.

11. The plug implant of claims 9to 10, wherein the material is prepared by layering PLC filaments layer by layer by using the Fused Deposition Modeling (FDM) technology.

12. The plug implant of claims 9-11, wherein the PLC filament layers have an orientation of 0 degree, 60 degree and/or 120 degree.

13. The plug implant of claims 1-12, wherein the wherein the expandable material comprises bioresorbable tricalcium phosphate-polycaprolactone (TCP-PLC).

14. The plug implant of claim 13, wherein the TCP-PLC is TCP-PLC 20:80%.

15. The plug implant of claims 13-14, wherein the TCP-PLC has 60-70% of porosity.

16. The plug implant of claims 1-15, wherein the plug implant comprises an opening for placement and removal of a catheter.

17. The plug implant of claims 1-16, wherein the plug implant expands at contact with hydrophilic solution, hydrophilic liquid and/or body fluid.

18. The plug implant of claims 1-17, wherein the plug implant is suitable to be inserted into a defect of a bone and the plug implant does not require means for fixing the plug to the external surface of the bone.

19. The plug implant of claims 1-18, further comprising a bioactive agent.

20. The plug implant of claims 1-19, further comprising cells seeded on the bioabsorbable scaffold of the plug implant.

21. The plug implant of claim 20, wherein the cells are stem cells.

22. The plug implant of claims 20-21, wherein the cells are mesenchymal stem cells.

23. A bioabsorbable plug implant, suitable for bone tissue regeneration, formed from expandable material, wherein the expandable material is prepared by layering polycaprolactone (PLC) filaments layer by layer.

24. The bioabsorbable plug implant of claim 23, comprising a first portion, and a second portion extending outwardly from the first portion, the first and second portions formed from expandable material.

25. The plug implant of claims 23 to 24, wherein the plug implant is shaped like a cone, truncated-cone, a pentahedron, a truncated-pentahedron, and/or a button mushroom.

26. The plug implant of claims 24 to 25, wherein the first portion comprises a first surface, and the second portion comprises a second surface, opposite to the first, the first surface having an area smaller than the area of the second surface.

27. The plug implant of claims 24 to 26, wherein the first and second surface are plane surfaces.

28. The plug implant of claims 24 to 27, wherein the first and the second surfaces have circular, square or rectangular shapes.

29. The plug implant of claims 23 to 28, wherein the plug implant has a tapered shape.

30. The plug implant of claims 24 to 29, wherein the first portion has a thickness X, and the second portion has a thickness Y, the ratio X:Y being from 1:1 to 10:1

31. The plug implant of claims 23 to 30, wherein the expandable material is a porous material.

32. The plug implant of claims 23 to 31, wherein the plug implant has a completely interconnected porous architecture.

33. The plug implant of claims 23 to 32, wherein the expandable material is prepared by layering PLC filaments layer by layer by using the Fused Deposition Modeling (FDM) technology.

34. The plug implant of claims 23 to 33, wherein the PLC filament layers have an orientation of 0 degree, 60 degree and/or 120 degree.

35. The plug implant of claims 23 to 34, wherein the wherein the expandable material comprises bioresorbable tricalcium phosphate-polycaprolactone (TCP-PLC).

36. The plug implant of claim 35, wherein the TCP-PLC is TCP-PLC 20:80%.

37. The plug implant of claims 35 to 36, wherein the TCP-PLC has 60-70% of porosity.

38. The plug implant of claims 23 to 37, wherein the plug implant comprises an opening for placement and removal of a catheter.

39. The plug implant of claims 23 to 38, wherein the plug implant expands at contact with hydrophilic solution, hydrophilic liquid and/or body fluid.

40. The plug implant of claims 23 to 39, wherein the plug implant is suitable to be inserted into a defect of a bone and the plug implant does not require means for fixing the plug to the external surface of the bone.

41. The plug implant of claims 23 to 40, further comprising a bioactive agent.

42. The plug implant of claims 23 to 41, further comprising cells seeded on the bioabsorbable scaffold of the plug implant.

43. The plug implant of claim 42, wherein the cells are stem cells.

44. The plug implant of claims 42 to 43, wherein the cells are mesenchymal stem cells.

45. A method for bone tissue regeneration comprising the steps of:

providing a bioabsorbable plug implant, wherein the implant comprises a first portion and a second portion extending outwardly from the first portion, the first and second portions formed from expandable material, and wherein the expandable material is a porous material;

inserting the first portion into a defect or gap of a bone, the second portion engaging the outside contour of the defect or gap;

allowing the plug implant to contact body fluids, thereby expanding the size of the plug implant so that the plug fits into the defect or gap.

46. The method of claim 45, wherein the implant comprises a first and a second surface, opposite to each other, the first surface having an area smaller than the area of the second surface.

47. The method of claims 45 to 46, wherein the plug implant is shaped like a cone, truncated-cone, a pentahedron, a truncated-pentahedron, and/or a button mushroom.

48. The method of claims 45 to 47, wherein the first and second surface are plane surfaces.

49. The method of claims 45 to 48, wherein the first and the second surfaces have circular, square or rectangular shapes.

50. The method of claims 45 to 49, The method of claim 45, wherein the plug implant has a completely interconnected porous architecture.

51. The method of claims 45 to 50, wherein the plug implant is formed from a porous material allowing the bone cells to penetrate into the plug implant and to regenerate the bone tissue.

52. The method of claims 45 to 51, which is a method for performing cranioplasty.

53. The method of claims 45 to 52, wherein plug implant and the bone defect or gap have an initial tolerance of less than 1 mm.

54. The method of claim 53, wherein the initial tolerance is less than 0.5 mm.

55. The method of claim 53, wherein the initial tolerance is less than 0.2 mm.

56. The method of claims 45 to 55, wherein the first portion has a thickness X, and the second portion has a thickness Y, the ratio X:Y being from 1:1 to 10:1.

57. The method of claims 45 to 56, wherein the expandable material comprises bioresorbable polycaprolactone (PLC).

58. The method of claim 57, wherein the expandable material is prepared by layering PLC filaments layer by layer.

59. The method of claims 57 to 58, wherein the material is prepared by layering PLC filaments layer by layer by using the Fused Deposition Modeling (FDM) technology.

60. The method of claims 57 to 59, wherein the PLC filament layers have an orientation of 0 degree, 60 degree and/or 120 degree.

61. The method of claims 45 to 60, wherein the expandable material comprises bioresorbable tricalcium phosphate-polycaprolactone (TCP-PLC).

62. The method of claim 61, wherein the TCP-PLC is TCP-PLC 20:80%.

63. The method of claims 61 to 62, wherein the TCP-PLC has 60-70% of porosity.

64. The method of claims 45 to 63, further comprising placing catheter into an opening of the plug implant for performing drainage.

65. The method of claims 45 to 64, wherein the insertion of the plug implant into the bone defect does not require means for fixing the plug to the external surface of the bone surrounding the defect.

66. The method of claims 45 to 65, wherein the method is a non therapeutic method for the cosmetic restoration of undesirable osseous gaps.

67. The method of claims 45 to 66, wherein the plug implant further comprising a bioactive agent.

68. The method of claims 45 to 67, wherein the plug implant further comprising cells seeded on the bioabsorbable scaffold of the plug implant.

69. The method of claim 68, wherein the cells are stem cells.

70. The method of claims 68 to 69, wherein the cells are mesenchymal stem cells.

71. A method for bone tissue regeneration comprising the steps of:

providing a bioabsorbable plug implant according to any one of claims 23 to 44;

inserting a first portion of the plug implant into a defect or gap of a bone, a second portion of the plug implant engaging the outside contour of the defect or gap;

allowing the plug implant to contact body fluids, thereby expanding the size of the plug implant so that the plug fits into the defect or gap.

72. The method of claim 71, wherein the plug implant is formed from a porous material allowing the bone cells to penetrate into the plug implant and to regenerate the bone tissue.

73. The method of claims 71 to 72, which is a method for performing cranioplasty.

74. The method of claims 71 to 73, wherein plug implant and the bone defect or gap have an initial tolerance of less than 1 mm.

75. The method of claim 74, wherein the initial tolerance is less than 0.5 mm.

76. The method of claim 74, wherein the initial tolerance is less than 0.2 mm.

77. The method of claims 71 to 76, further comprising placing catheter into an opening of the plug implant for performing drainage.

78. The method of claims 71 to 77, wherein the insertion of the plug implant into the bone defect does not require means for fixing the plug to the external surface of the bone surrounding the defect.

79. The method of claims 71 to 78, wherein the method is a non therapeutic method for the cosmetic restoration of undesirable osseous gaps.

80. The method of claims 71 to 79, wherein the plug implant further comprises seeding cells on the bioabsorbable scaffold of the plug implant.

81. The method of claim 80, wherein the cells are stem cells.

82. The method of claims 80 to 81, wherein the cells are mesenchymal stem cells.

83. A kit comprising the plug implant of claims 1to 44.